

ANSWER 3 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1996:186710 CAPLUS

DOCUMENT NUMBER: 124:278432

TITLE: Inflammatory and immunological parameters of disease activity in rheumatoid arthritis patients treated with minocycline

AUTHOR(S): Kloppenburg, Margreet; Dijkmans, Ben A. C.; Verweij, Cor L.; Breedveld, Ferdinand C.

CORPORATE SOURCE: Department of Rheumatology, Leiden University Hospital, Building 1, C4-R, P.O. Box 9600, RC Leiden, 2300, Neth.

SOURCE: Immunopharmacology (1996), 31(2-3), 163-9

CODEN: IMMUDP; ISSN: 0162-3109

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The objective of this study was to analyze the anti-inflammatory effect of minocycline in rheumatoid arthritis. Serum samples of 65 RA patients who completed a 26-wk randomized double-blind trial of minocycline (100 mg twice a day) vs. placebo were studied. In this trial some clin. parameters and, in particular, the acute-phase response decreased significantly in the minocycline-treated group. Serum levels of albumin and interleukin-6 (IL-6) were compared with CRP levels in order to study the acute-phase response. Furthermore, rheumatoid factor (RF) and total Ig isotypes as well as serum levels of soluble interleukin-2 receptor (sIL2-2R) were determined in order to study immunol. parameters of the disease. Igs and cytokines were measured by ELISA. Serum levels of albumin remained stable, whereas serum CRP levels decreased both in the minocycline- and in the placebo-treated group. Serum levels of IL-6 decreased in the minocycline-treated group only and this decrease was pos. correlated with the decrease in CRP levels. Minocycline significantly decreased serum IgM-RF, IgA-RF, total IgM and total IgA levels. In addition the ratio of IgM-RF/total IgM decreased in the minocycline-treated group. No such changes were observed in the placebo-treated group. The anti-inflammatory effect of minocycline in RA patients may be due to the reduction in the synthesis of IL-6 and rheumatoid factor.

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ANSWER 11 OF 38 USPATFULL on STN

ACCESSION NUMBER: 2003:159805 USPATFULL  
TITLE: Diagnostic markers of acute coronary syndrome and  
methods of use thereof  
INVENTOR(S): Valkirs, Gunars, Escondido, CA, UNITED STATES  
Dahlen, Jeffrey, San Diego, CA, UNITED STATES  
Buechler, Kenneth F., Rancho Santa Fe, CA, UNITED  
STATES  
Kirchick, Howard J., San Diego, CA, UNITED STATES  
PATENT ASSIGNEE(S): Biosite, Inc. (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003109420	A1	20030612	<--
APPLICATION INFO.:	US 2002-139086	A1	20020504 (10)	

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-288871P	20010504 (60)
	US 2001-315642P	20010828 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	FOLEY & LARDNER, P.O. BOX 80278, SAN DIEGO, CA, 92138-0278	
NUMBER OF CLAIMS:	68	
EXEMPLARY CLAIM:	1	
LINE COUNT:	4194	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to methods for the diagnosis and evaluation of acute coronary syndromes. In particular, patient test samples are analyzed for the presence and amount of members of a panel of markers comprising one or more specific markers for myocardial injury and one or more non-specific markers for myocardial injury. A variety of markers are disclosed for assembling a panel of markers for such diagnosis and evaluation. In various aspects, the invention provides methods for the early detection and differentiation of stable angina, unstable angina, and myocardial infarction. Invention methods provide rapid, sensitive and specific assays that can greatly increase the number of patients that can receive beneficial treatment and therapy, reduce the costs associated with incorrect diagnosis, and provide important information about the prognosis of the patient.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 2003109420 A1 20030612 <--  
SUMM [0004] ACS is a manifestation of vascular injury to the heart, also referred to as myocardial injury or myocardial damage, that is commonly secondary to atherosclerosis or hypertension, and is the leading cause of death in the United States. ACS is commonly caused by occlusion associated with coronary artery disease cause by atherosclerotic plaque formation and progression to either further occlusion or fissure. ACS can be

Sensitivity and specificity of. . .

DETD [0191] The observation that MMP-9, cTnI, BNP, and CRP are each independently associated with 10-month patient mortality indicates that multi-marker testing strategies in patients with suspected ACS can advantageously. . . therapies to different underlying pathophysiologic mechanisms. This "risk profile" may be determined by various combinations of MMP-9, cTnI, BNP, and CRP, as well as by other markers used in addition to or substituted for said markers.

DETD [0192] Additionally, markers such as MMP-9 that play a direct pathogenic role in atherosclerosis and its complications can provide novel therapeutic targets for drug discovery. For example, the MMP system might be regulated on. . . proenzyme activation, and inhibition by tissue inhibitors of metalloproteinases (TIMPs). Modification of one or more of these steps may prevent atherosclerotic plaque rupture and modify adverse vascular and cardiac remodeling.

DETD . . . composition directed to MMP-9 or a fragment thereof); and/or delivery of small molecule therapeutics (e.g., heparin can decrease MMP-9 synthesis, tetracycline antibiotics can inactivate MMPs by chelating zinc, and HMG Co-A Reductase inhibitors and activators of Peroxisomal Proliferator-Activator Receptor (PPAR)-gamma can. . .

CLM What is claimed is:

. . . are selected from the group consisting of an MMP-9 level, a Ttp level, an MCP-1 level, an H-FABP level, a CRP level, a creatine kinase level, an MB isoenzyme level, a cardiac troponin I level, a cardiac troponin T level, and a level of complexes comprising cardiac troponin I and cardiac troponin T.

. . . wherein said specific marker for myocardial injury is selected from the group consisting of annexin V, B-type natriuretic peptide,  $\beta$ -enolase, cardiac troponin I, creatine kinase-MB, glycogen phosphorylase-BB, heart-type fatty acid binding protein, phosphoglyceric acid mutase-MB, and S-100ao.

. . . to claim 41, wherein said non-specific marker for myocardial injury is selected from the group consisting of a marker of atherosclerotic plaque rupture, a marker of coagulation, C-reactive protein, caspase-3, hemoglobin  $\alpha$ .sub.2, human lipocalin-type prostaglandin D synthase, interleukin-1 $\beta$ , interleukin-1 receptor antagonist, interleukin-6, monocyte chemotactic protein-1, soluble intercellular adhesion molecule-1,. . .

44. A method according to claim 43, wherein said marker of atherosclerotic plaque rupture is selected from the group consisting of human neutrophil elastase, inducible nitric oxide synthase, lysophosphatidic acid, malondialdehyde-modified low. . .

. . . of one or more markers selected from the group consisting of matrix metalloprotease-9 (MMP-9), an MMP-9-related marker, Ttp, MCP-1, H-FABP, C-reactive protein, creatine kinase, MB isoenzyme, cardiac troponin I, cardiac troponin T, complexes comprising cardiac troponin I and cardiac troponin T, and B-type natriuretic protein in a sample obtained from said patient to said patient prognosis by determining if. . .

. . . according to claim 60, wherein said adverse outcome is selected from the group consisting of death, myocardial infarction, and congestive heart failure.

. . . of two or more markers selected from the group consisting of matrix metalloprotease-9 (MMP-9), an MMP-9-related marker, Ttp, MCP-1, H-FABP, C-reactive protein, creatine kinase, MB isoenzyme, cardiac troponin I, cardiac troponin T, complexes comprising cardiac troponin I and cardiac troponin T, and B-type natriuretic protein in a sample obtained from

ACCESSION NUMBER: 2001:377301 BIOSIS  
DOCUMENT NUMBER: PREV200100377301  
TITLE: The effects of intravenous doxycycline therapy for  
rheumatoid arthritis: A randomized, double-blind,  
placebo-controlled trial.  
AUTHOR(S): St.Clair, E. William [Reprint author]; Wilkinson, William  
E.; Pisetsky, David S.; Sexton, Daniel J.; Drew, Richard;  
Kraus, Virginia B.; Greenwald, Robert A.  
CORPORATE SOURCE: Duke University Medical Center, Durham, NC, 27710, USA  
SOURCE: Arthritis and Rheumatism, (May, 2001) Vol. 44,  
No. 5, pp. 1043-1047. print.  
CODEN: ARHEAW. ISSN: 0004-3591.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
ENTRY DATE: Entered STN: 8 Aug 2001  
Last Updated on STN: 19 Feb 2002

AB Objective: To determine the feasibility, safety, and potential clinical  
efficacy of intravenous (IV) doxycycline therapy for rheumatoid  
arthritis (RA), as well as its possible effects on serum and  
urinary markers of collagen breakdown. Methods: The exploratory trial was  
designed as a 16-week, single-center, randomized, double-blind,  
placebo-controlled trial. Eligible subjects with active seropositive or  
erosive RA were randomly allocated into 3 treatment groups:  
doxycycline 200 mg IV, azithromycin 250 mg orally, or placebo. The  
blinded IV study drug was administered once daily for the first 3 weeks by  
home self-infusion and then weekly for the next 8 weeks, concurrent with  
the blinded oral study drug at the prescribed doses. The primary end  
points were the change between baseline and week 4 in the tender joint  
count, erythrocyte sedimentation rate, and urinary excretion of  
pyridinoline. Results: The trial was stopped prematurely after enrollment  
of 31 patients. Three subjects were withdrawn because of worsening  
arthritis, and 1 patient was withdrawn when newly diagnosed with  
breast cancer. Infusion-related events occurred in 13 (42%) of 31  
patients, but none were serious. There were 4 serious adverse events  
unrelated to the study drug, including a new diagnosis of breast cancer in  
3 cases and hospitalization for abdominal pain in 1 case. No significant  
differences were observed across treatment groups in any of the  
3 primary clinical end points. Conclusion: Although IV doxycycline  
therapy was generally well-tolerated by patients in this trial, it did not  
show any evidence of reducing disease activity or collagen crosslink  
production.

TI The effects of intravenous doxycycline therapy for rheumatoid  
arthritis: A randomized, double-blind, placebo-controlled trial.

SO Arthritis and Rheumatism, (May, 2001) Vol. 44, No. 5, pp.  
1043-1047. print.

CODEN: ARHEAW. ISSN: 0004-3591.

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blinded IV study drug was administered once daily. . . of pyridinoline.  
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arthritis, and 1 patient was withdrawn when newly diagnosed with  
breast cancer. Infusion-related events occurred in 13 (42%) of 31  
patients,. . . of breast cancer in 3 cases and hospitalization for  
abdominal pain in 1 case. No significant differences were observed across  
treatment groups in any of the 3 primary clinical end points.

ACCESSION NUMBER: 2000:232964 BIOSIS  
DOCUMENT NUMBER: PREV200000232964  
TITLE: beta2-Microglobulin induces MMP-1 but not TIMP-1 expression  
in human synovial fibroblasts.  
AUTHOR(S): Moe, Sharon M. [Reprint author]; Singh, Gurinder K.  
[Reprint author]; Bailey, Anna M. [Reprint author]  
CORPORATE SOURCE: Division of Nephrology, Indiana University School of  
Medicine and Richard Roudebush Veterans Administration  
Medical Center, Indianapolis, IN, USA  
SOURCE: Kidney International, (May, 2000) Vol. 57, No. 5,  
pp. 2023-2034. print.  
CODEN: KDYIA5. ISSN: 0085-2538.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
ENTRY DATE: Entered STN: 7 Jun 2000  
Last Updated on STN: 5 Jan 2002

AB Background: beta2-Microglobulin (beta2m) amyloidosis is a destructive  
articular disease that causes significant morbidity in patients undergoing  
hemodialysis. The amyloid deposits contain beta2m, some of which is  
altered with advanced glycation end products (AGE-beta2m). The deposits  
are located principally in joint structures, with adjacent degradation of  
cartilage and bone. We hypothesized that one of the mechanisms by which  
beta2m induces joint destruction is to induce the release of matrix  
metalloproteinase-1 (MMP-1), but not tissue inhibitor of  
metalloproteinase-1 (TIMP-1), from synovial fibroblasts. Methods: To test  
this hypothesis and determine the role of AGE-beta2m, we incubated human  
osteoarthritic synovial fibroblasts in the presence and absence of beta2m  
and AGE-beta2m and measured the release of interstitial collagenase  
(MMP-1) and/or TIMP-1 by enzyme-linked immunosorbent assay and Northern  
blot analysis. Results: beta2m and AGE-beta2m at 10 and 25 mug/mL induced  
the release of MMP-1 from human osteoarthritic synovial fibroblasts at 24  
hours. In contrast, there was no increased release of TIMP-1, leading to  
an increase in the MMP-1/TIMP-1 ratio indicative of uncontrolled  
collagenolysis. A similar dose response was observed at 48 hours, except  
that AGE-beta2m had no effect over control cultures. MMP-1 mRNA  
expression by Northern blot analysis paralleled these findings. The  
source of the fibroblasts did not alter the results. Finally, we  
demonstrated that doxycycline, a treatment for arthritis  
, can inhibit the release of MMP-1 from synovial fibroblasts incubated  
with beta2m. Conclusion: beta2m, at physiologically relevant  
concentrations, induces the release of MMP-1 without concomitant release  
of TIMP-1 from human synovial fibroblasts, leading to uncontrolled  
collagenolysis. The alteration of beta2m with AGE did not alter this  
effect at 24 hours, but blocked the effect at 48 hours. These findings  
may account for the tissue destruction seen in beta2m amyloidosis.

SO Kidney International, (May, 2000) Vol. 57, No. 5, pp. 2023-2034.  
print.

CODEN: KDYIA5. ISSN: 0085-2538.

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treatment for arthritis, can inhibit the release of  
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beta2m, at physiologically relevant concentrations, induces the. . .

RN 564-25-0 (doxycycline)  
9001-12-1 (interstitial collagenase)  
9001-12-1 (matrix metalloproteinase-1)  
9001-12-1 (MMP-1)  
140208-24-8 (tissue inhibitor of metalloproteinase-1)  
140208-24-8 (TIMP-1)

ACCESSION NUMBER: 2001:5497 BIOSIS  
DOCUMENT NUMBER: PREV200100005497  
TITLE: Long-term treatment with subantimicrobial dose  
doxycycline exerts no antibacterial effect on the  
subgingival microflora associated with adult periodontitis.  
AUTHOR(S): Walker, Clay [Reprint author]; Thomas, John; Nango, Sonia;  
Lennon, Jennifer; Wetzell, Jeanne; Powala, Christopher  
CORPORATE SOURCE: Health Science Center, University of Florida, Gainesville,  
FL, 32610, USA  
walkercl@ufl.edu  
SOURCE: Journal of Periodontology, (September, 2000) Vol.  
71, No. 9, pp. 1465-1471. print.  
CODEN: JOPRAJ. ISSN: 0022-3492.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
ENTRY DATE: Entered STN: 21 Dec 2000  
Last Updated on STN: 21 Dec 2000

AB Background: The purpose of this study was to determine whether treatment with subantimicrobial dose doxycycline (SDD), 20 mg bid, exerted an antimicrobial effect on the microflora associated with adult periodontitis. Methods: Following the approval of the protocol and informed consent forms by the respective IRBs at the University of Florida and West Virginia University, 76 subjects with adult periodontitis were entered and randomly assigned to receive SDD or placebo. A split-mouth design was utilized, with each subject receiving subgingival scaling and root planing (SRP) in two quadrants immediately following baseline data collection, while the remaining two quadrants were left unscaled (non-SRP). Microbial samples were collected prior to treatment, after 3, 6, and 9 months of treatment, and after 3 months of no treatment. The samples were examined by microscopy and by enumeration on selective and non-selective media. Results: All treatments resulted in statistically significant decreases in the proportions of spirochetes and motile rods ( $P < 0.05$ ) and in an increase in the proportion of coccoid forms ( $P < 0.0001$ ) relative to baseline. No between-treatment differences were detected between the SDD and placebo treatments in either the SRP or non-SRP design, with the exception of the small and large spirochetal groups. The spirochetal proportions present in the SDD group were significantly lower ( $P < 0.05$ ) than the paired placebo group during the 9-month treatment and was preceded by a significant decrease ( $P < 0.01$ ) in the proportion of microbiologic sample sites that bled on probing. No between-treatment differences were detected in any of the other microbial parameters. Conclusion: The microbial differences observed were attributed to the anticollagenase and anti-inflammatory properties of SDD and not to an antimicrobial effect.

TI Long-term treatment with subantimicrobial dose doxycycline exerts no antibacterial effect on the subgingival microflora associated with adult periodontitis.

SO Journal of Periodontology, (September, 2000) Vol. 71, No. 9, pp. 1465-1471. print.  
CODEN: JOPRAJ. ISSN: 0022-3492.

AB Background: The purpose of this study was to determine whether treatment with subantimicrobial dose doxycycline (SDD), 20 mg bid, exerted an antimicrobial effect on the microflora associated with adult periodontitis. Methods: . . . immediately following baseline data collection, while the remaining two quadrants were left unscaled (non-SRP). Microbial samples were collected prior to treatment, after 3, 6, and 9 months of treatment, and after 3 months of no treatment. The samples were examined by microscopy and by enumeration on selective and non-selective media. Results: All treatments resulted in statistically significant decreases in the proportions of spirochetes and motile rods ( $P < 0.05$ ) and in an increase

in the proportion of coccoid forms ( $P < 0.0001$ ) relative to baseline. No between-treatment differences were detected between the SDD and placebo treatments in either the SRP or non-SRP design, with the exception of the small and large spirochetal groups. The spirochetal proportions present in the SDD group were significantly lower ( $P < 0.05$ ) than the paired placebo group during the 9-month treatment and was preceded by a significant decrease ( $P < 0.01$ ) in the proportion of microbiologic sample sites that bled on probing. No between-treatment differences were detected in any of the other microbial parameters. Conclusion: The microbial differences observed were attributed to the anticollagenase and anti-inflammatory properties of SDD and not to an antimicrobial effect.

IT . . .  
    (Human Medicine, Medical Sciences); Pharmacology  
IT Diseases  
    adult periodontitis: dental and oral disease  
IT Chemicals & Biochemicals  
    doxycycline: anti-collagenase effect, anti-inflammatory  
    effect, long-term treatment, subantimicrobial dose  
RN 564-25-0 (doxycycline)